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Is Hemoglobinuric Fever a Manifestation of Malaria or a Disease *Sui Generis?*

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IS HEMOGLOBINURIC FEVER A MANIFESTATION OF MALARIA OR A DISEASE *SUI GENERIS*?*

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The present condition of uncertainty regarding the etiology of hemoglobinuric fever may well be likened to that regarding the etiology of kala-azar ten years ago, and the history in this respect of the latter disease is of peculiar interest to the students of hemoglobinuric fever, because it furnishes an excellent example of how preconceived opinions influence the work of careful observers, and illustrates the fallibility of deductions regarding the etiology of any disease when influenced by such opinions.

For many years kala-azar was regarded as a persistent form of malarial infection, or a form of malarial cachexia. As late as 1896 Leonard Rogers considered it to be a fatal form of malaria, while Ronald Ross, in 1898, stated it as his belief that it was a form of malarial fever complicated by some secondary infection. Giles, after careful study, had come to the conclusion that kala-azar was due to *Ankylostoma duodenale,* and Bentley, in 1903, regarded it as a severe form of Malta fever. The discovery of the parasite now known as *Leishmania donovani* by Leishman, which was at once confirmed by Donovan, decided the etiology of kala-azar, and proved how erroneous were the theories regarding its malarial origin.

For years the study of hemoglobinuric fever has been greatly influenced by the theory that it is due to malarial infection, and much of the data which has accumulated concerning this disease has been published by believers in the malarial theory, or in the theory that it is due to quinin. While the literature contains many authentic instances which absolutely disprove both of these theories their adherents appear to have overlooked or undervalued them, and to-day the general opinion of the medical profession appears to be in favor of the theory that hemoglobinuric fever is due to malarial infection.

To one who carefully studies the literature of this disease it is evident that, in reality, its etiology is unknown; that the preconceived opinions regarding its malarial nature and its relation to quinin have greatly hindered investigation, and influenced those who have endeavored to study its etiology from an experimental standpoint; and that there is

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*Read at the seventh annual meeting of the American Society of Tropical Medicine, June 11, 1910. Published by authority of the Surgeon General, U. S. Army.

every reason to believe that further research will result in proving that hemoglobinuric fever is a specific disease. The further we inquire into its etiology, pathology, and symptomatology, the more must we become convinced that the malarial nature of the condition is far from demonstrated, and that the evidence points to its being a specific disease caused by an undiscovered parasite.

Before considering in detail the theories regarding the etiology of this disease, I desire to call attention to the fact that not a few of the cases reported in the literature as hemoglobinuric fever are in reality other forms of hemoglobinuria or hematuria, having no relation to the true disease. Therefore, in the study of this condition it is most important to be sure that we are dealing with true hemoglobinuric fever rather than other conditions which sometimes very closely simulate it. Thus we must differentiate paroxysmal hemoglobinuria, hematuria, the hemoglobinuria following the administration of poisonous drugs, and the rare instances of idiosyncrasy to quinin, resulting in the production of this symptom. True hemoglobinuric fever has a definite symptomatology and is readily recognized by those living in the endemic areas, and all cases which do not agree with the clinical characteristics which have been described by many careful observers in blackwater fever regions should be regarded with suspicion. The mere fact that a patient passes a little bloody urine is very insufficient proof that he is suffering from hemoglobinuric fever, and yet the literature contains numerous reports in which this was the only symptom present, and such cases have been used to support the several theories regarding the etiology of the disease. In this contribution I have been careful to cite only those reports in which the patients described were without doubt suffering from hemoglobinuric fever.

There are three principal theories regarding the etiology of this disease; first, that it is due directly or indirectly to malarial infection; second, that it is due to quinin; and third, that it is a specific disease. Each has its enthusiastic supporters, but, as a matter of fact, not one of them rests on a firm foundation as regards absolute proof.

1. THE MALARIAL THEORY

PRESENT STATUS OF THEORY

The theory that hemoglobinuric fever is due directly or indirectly to malarial infection is very old, and is supported by many of the greatest authorities on the fevers of tropical and subtropical countries. The names of Plehm, Stephens, Bentley, Christophers, Zieman, Mannaberg, and others of equal reputation, are associated with this theory, and the following quotations from Stephens well illustrate its present position. Stephens says:[1]

1. Stephens, J. W. W.: Blackwater Fever, in Allbutt and Rolleston's A System of Medicine, London, 1907, ii, part 2, p. 295.

The etiology of blackwater fever may be summed up by saying that it is malarial in nature, *i. e.*, that it can only occur in those who are either suffering from, or have quite recently become infected with, malaria, and that the onset of the disease is induced most commonly, though not invariably, by quinin.

Again, in another contribution, he says:[2]

We may sum up the etiology of blackwater fever somewhat in this way: It is not a disease *per se*, but rather a condition of blood in which quinin, other drugs, cold, or even exertion, may produce a sudden destruction of red cells. The condition is produced only by malaria, and generally by repeated small attacks, insufficiently treated by quinin. In such cases of chronic malaria (*i. e.*, in those suffering from anemia with repeated attacks of fever and repeated doses of quinin) blackwater fever sooner or later almost certainly supervenes, at least in tropical climates. The two main factors in hemoglobinuria are, then, malaria and quinin.

Because of the objections to the malarial theory which have arisen from time to time, its adherents have modified their views, until we now have the rather amusing spectacle of a theory supported by numerous authorities, each of whom, however, explains the relation of the two diseases in a different maner. That this is true is evidenced by the following modifications of the theory which are supported by different investigators: Hemoglobinuric fever is caused by estivo-autumnal plasmodia; it is caused by a special species of malarial plasmodium; it is a peculiar form of pernicious malaria, which may be produced by any one of the species of plasmodia; it is due to malignant tertian infection accompanied by congestion of the liver; it is due to a toxin produced by the malarial plasmodia; it is due to a toxin resulting from the destruction of the red corpuscles by the plasmodia; it is due to changes in the blood caused by previous malarial infection; it is due to a condition of susceptibility to quinin brought about by malarial infection; it is due to an autolysin produced in the blood by malarial infection; it is an idiosyncrasy of certain malarial patients; and, finally, it is simply a complication of malarial fever.

The points which are usually urged in support of the malarial theory of the origin of hemoglobinuric fever are the following:

1. The occurrence of the disease only in malarial regions.
2. The presence of plasmodia in the blood, during the period immediately preceding, or during the first days of an attack.
3. The fact that most patients who develop hemoglobinuric fever have suffered previously from malaria.
4. The more frequent occurrence of the disease in localities where pernicious forms of malaria occur.
5. The fact that long residence in a malarial locality is required before the disease can develop.
6. The fact that there is an increase in the large mononuclear leukocytes similar to that occurring in malarial infection.

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2. Stephens, J. W. W.: Blackwater Fever, in Osler's Modern Medicine, Philadelphia, 1907, i, 455.

In order to understand clearly the relation of malaria to hemoglobinuric fever, it is necessary to consider each of the points mentioned; and I believe that a careful survey of the evidence will carry the conviction that not one of them can be accepted as proving that the disease is of malarial origin, and that taken together they speak as strongly in support of the specific theory as they do of the theory under discussion.

THE GEOGRAPHICAL DISTRIBUTION OF HEMOGLOBINURIC FEVER AND MALARIA

It is an accepted fact that hemoglobinuric fever occurs only in regions where malarial infections are endemic, but does this prove that the disease is of malarial origin? While the disease occurs only where malarial infections are endemic, there are many regions intensely infected with malaria where this disease is unknown. This fact must be admitted by every student of the disease, and is most difficult of explanation, if we accept the malarial theory. Hemoglobinuric fever is very prevalent and wide-spread in Africa, common in Sicily and Sardinia, but rare in Italy. In India the disease occurs in very limited localities, and similar regions in that country, as regards climatic and other known conditions, and as intensely infected with malaria, are free from hemoglobinuric fever. In Italy, even in the regions where the malarial fevers are most pernicious, this disease is either absent, or occurs very rarely. In fact, it may be said that Africa is the only country in which hemoglobinuric fever is generally distributed, for, in all the other countries in which it occurs, its distribution is strictly localized, while there are many countries in which pernicious forms of malaria occur, but in which blackwater fever is unknown, or occurs only in the form of imported cases. In a personal letter Dr. Prado, health officer of Trinidad, informs me that while malaria is both prevalent and severe in Trinidad and the island of Tobago, blackwater fever is common in Tobago and very rare in Trinidad, occurring only on a part of the coast-line adjacent to Tobago, and frequented by laborers from that island.

Even in the countries in which this fever occurs, there are many regions as intensely infected with malaria which are free from the disease, although only a comparatively short distance from the endemic foci. Such regions occur in our own country, in some of the southern states, and in Italy hemoglobinuric fever is limited to very restricted localities, while some of the worst malarial portions of that country have never presented a single instance of this disease. The same is true of India, of the Straits Settlements, the islands of Polynesia, the West Indies, and the countries of South America.

The almost complete absence of hemoglobinuric fever in the Philippine Islands is an excellent illustration of the fact that a most malarial

country may be free from the disease. In the Philippine Census[3] for 1902, the total number of deaths from malarial fever is stated to have been 118,476, or 26.8 per cent. of all deaths, the death-rate being seventeen per thousand, and yet not a single death is recorded as being due to hemoglobinuric fever. How is it possible to explain this fact in accordance with the theory that the disease is caused by malarial infection?

Christophers and Bentley[4] believe that hemoglobinuric fever occurs only in countries where the malarial infections are intense, and that such infections, no matter what species of plasmodium causes them, may give rise to the disease. I believe that all will admit that the vast majority of intense or malignant malarial infections are caused by the estivo-autumnal plasmodia, but even in regions where the most severe estivo-autumnal infections are prevalent, hemoglobinuric fever is often absent. At Camp Stotsenburg, in the Philippines, one of the most intensely malarial regions of which we have record, where, within six months, there were more than thirty deaths from pernicious malaria among the natives in the vicinity, a case of hemoglobinuric fever has never been known to occur, and the natives informed me that they had never heard of a single instance of the passage of bloody urine during an attack of fever. If intense malarial infection is necessary for the production of hemoglobinuric fever, then in this locality one would expect to meet instances of the disease, but it is unknown. This is equally true of every other intensely malarious region in the Philippine Islands and of similar regions in many other parts of the world. Tables 1, 2 and 3 illustrate the intensity of malarial infection in some of the islands, provinces and towns of the Philippines, and prove that intensity of malarial infection has nothing to do with the production of hemoglobinuric fever.

It is evident from these tables that the Philippines are intensely infected with malaria and that the death-rate is high from that disease; but hemoglobinuric fever is practically unknown. I know from personal observation that the death-rate as given for some of these towns is not excessive, and that there are many towns in the Philippines in which malaria causes more than 50 per cent. of the death-rate.

Christophers and Bentley state that certain conditions may be present in blackwater regions which are not present in other malarial regions, but so far as climatic conditions are concerned this is not so, for in almost every country in which hemoglobinuric fever occurs the climatic conditions are the same in the blackwater regions as in others. So far as other conditions are concerned, it is enough to say that we are absolutely ignorant of what they are, and therefore they cannot be used in proving the malarial hypothesis. The fact remains that intense estivo-

3. Census of the Philippine Islands, Washington, 1905, iii, 70.

4. Christophers, S. R., and Bentley, C. A.: Blackwater Fever, Scient. Mem., Med. and San. Depts. Govt. India, Simla, 1908, N. S., No. 35.

TABLE 1.—TOTAL DEATHS AND DEATHS FROM MALARIA IN CERTAIN ISLANDS OF THE PHILIPPINES

Island.	Total Deaths.	Deaths from Malaria.
Luzon	248,831	60,516
Cebu	18,955	6,356
Panay	75,535	22,478
Mindanao	12,572	6,423
Marinduque	3,222	1,466
Guimaras	1,302	479
Baliran	1,247	423

TABLE 2.—POPULATION, TOTAL DEATHS AND DEATHS FROM MALARIA IN THE PROVINCES OF THE PHILIPPINE ISLANDS

Province.	Population.	Total Deaths.	Deaths from Malaria.	Pr. Ct. of All Deaths.
Albay	240,326	11,564	3,103	26.8
Antigue	134,166	7,411	3,181	42.9
Batangas	257,715	34,257	13,216	38.5
Capiz	230,721	15,564	3,254	20.9
Cebu	653,727	20,920	7,020	33.6
Iloilo	410,315	51,153	16,572	32.4
La Laguna	148,606	15,918	4,877	30.6
Misamis	175,683	9,038	4,961	54.9
Pampanga	223,754	14,383	3,247	22.6
Pangasinan	397,902	24,701	6,531	26.4
Samar	266,237	13,614	3,913	28.7
Tayabas	153,065	9,418	3,501	37.2
Davao	65,496	557	256	46.
Marinduque	51,674	3,222	1,466	45.
Masbate	43,675	1,881	811	43.1
Nueva Vizcaya	62,541	1,228	511	41.6
Dapitan	23,577	397	152	38.3
Romblon	52,848	1,422	531	37.3
Surigao	115,112	3,304	1,200	36.3
Negros Oriental	201,494	5,972	2,135	35.8
Tarlao	135,107	7,088	2,453	34.6

TABLE 3.—POPULATION, TOTAL DEATHS AND DEATHS FROM MALARIA IN PHILIPPINE TOWNS *

Town.	Population.	Total Deaths.	Deaths from Malaria.
Angeles	10,646	431	119
Apalit	12,206	771	208
Anao-aon	1,481	90	59
Bacuag	2,938	100	77
Camiling	25,243	1,288	513
Concepcion	12,593	600	211
Gerona	13,615	635	257
Floridablanca	7,001	623	328
Jiminez	7,187	1,066	1,019
Misamis	5,525	310	290
Mabalacat	7,009	201	126
Mainit	1,588	123	84
Orequita	15,156	1,650	1,572
Palapag	9,609	200	122
Pasig	4,830	296	110
Pambujan	6,439	331	174
Porac	8,487	490	251
San Carlos	27,166	1,856	744
Tago	3,298	129	60
Taranguan	6,184	549	234
Tigao	946	16	8
Urdaneta	20,544	1,378	498

* All of these tables are compiled from the Philippine Census.

autumnal infections are prevalent in nearly all tropical regions, while hemoglobinuric fever is restricted to certain countries, and in these countries, as a general rule, it occurs only in limited localities.

In regions in which hemoglobinuric fever occurs, the disease may be limited to certain very small areas, even to certain houses, and so-called "blackwater fever houses" have been reported by Daniels, Christophers and Bentley, and others. Christophers and Bentley report instances in which two or more cases of the disease have occurred in the same house, while other houses in the vicinity remained free from the infection. Because these houses were located in malarial localities, these authors believe that the disease must have been of malarial origin, but it would appear more reasonable to believe that some specific cause was present in these houses, or that the transmitting agent, perhaps a comparatively rare insect, was to be found only in the houses mentioned.

Another fact that speaks against the theory that hemoglobinuric fever is of malarial origin is that, in some of the countries where it is now prevalent, it has only recently been observed, although malarial fevers have been present for centuries. This fact must be admitted by every one who is conversant with the literature of the disease. A. Plehn[5] states that it is only recently that the disease has appeared on the west coast of Africa, where it is increasing in frequency yearly; and the same is true of India, where it is now prevalent in limited localities. The very extensive and valuable works of such men as Carter and Fayrer contain no mention of the occurrence of this disease in India in their time, and it is impossible to believe that these keen clinical observers could have overlooked a disease so striking in its symptomatology as is hemoglobinuric fever. If, then, this fever be due to malaria, how is it possible to explain its recent appearance in countries where for centuries the most intense malarial infections have existed? While it must be admitted that the disease occurs only in malarial localities, it can by no means be admitted that, therefore, the disease is of malarial nature. Many other acute infectious diseases are most commonly observed in regions infected with malaria, such as amebic dysentery, beriberi, infections with the various intestinal parasites, yellow fever, kala-azar, sleeping-sickness, and most tropical diseases, and some of them are practically limited to malarial localities, especially kala-azar, sleeping-sickness, and yellow fever; but we do not for this reason conclude that they are caused by malarial infection. The absence of hemoglobinuric fever from many intensely malarial regions and its presence in very limited localities in the regions in which it does occur, together with its recent appearance in certain countries, is very strong presumptive evidence that it is not due to

5. Plehn, A.: The Cause, Prevention and Treatment of Hemoglobinuric Fever in Warm Countries, Jour. Trop. Med. and Hyg., 1908, ii, 294.

malaria, and I believe that the unprejudiced observer must admit that the geographical distribution of this disease, far from proving its malarial origin, points directly to its specific nature.

LENGTH OF RESIDENCE AND HEMOGLOBINURIC FEVER

It is a well-known fact that most victims of hemoglobinuric fever have resided for some time in the infected locality, and this fact is used as an argument in favor of the malarial theory, it being claimed that repeated malarial attacks are necessary for the production of this disease, and that therefore long residence in a malarial locality is essential. While it must be admitted that most cases of hemoglobinuric fever occur after the first twelve months of residence in the infected district is completed, many instances have been reported in which the symptoms appeared within less than three months after entering the infected territory, and in individuals who had never suffered from malarial infection, so far as could be ascertained; while a few cases have been reported in which the disease appeared within a few days after entering the blackwater district. I shall mention only a few of the authors who have reported instances of this kind, but the literature contains a great many such cases. Poole[6] found that, of fifty-six cases studied by him, no less than seventeen occurred in individuals who had been in the infected district less than one year. Reynolds[7] describes one instance in which the patient developed the disease within ten weeks after reaching the infected region, and others in which the disease appeared in four months, seven months, and nine months. Berenger-Feraud[8] observed one case in which the disease developed within three months, and ten in which it developed within one year; while Christophers and Bentley[4] observed one case developing within six months, and eight within one year after exposure in infected districts. Manson[9] states that instances of infection have been observed during the second and third months after arrival in infected regions, and in the last edition of his work on tropical diseases, he says (p. 235):

> There are many cases on record in which blackwater fever occurred before any kind of "malaria" had manifested itself. Plehn, Scott, Ritchie, Cardamatis, Lynch, Hearsey, Daniels and others have reported cases of blackwater fever in robust, healthy individuals, who were attacked within two or three months of their arrival in a blackwater fever country. I have frequently been told by officers in the African colonial service that the attack of blackwater fever for which they were invalided suddenly developed while they appeared to be in perfect health and without any malarial antecedents.

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6. Poole, W.: An Analysis of Fifty-six Cases of Blackwater Fever, Jour. Trop. Med., 1899, i, 145.

7. Reynolds, G. F.: Blackwater Fever, Some Cases and Notes, Jour. Trop. Med., 1899, i, 16.

8. Berenger-Feraud: De la fièvre bileuse mélanurique des pays chauds, Paris, 1874, Ed. I.

9. Manson, Sir Patrick: Tropical Diseases, New York, 1907, Ed. 4.

F. Plehn[10] saw two patients suffering from hemoglobinuric fever which developed within four or five weeks after their arrival in Cameroon, neither of whom had suffered from malarial infection. Gross saw a patient who developed the disease within fifteen days after reaching Gaboon, and who had never had malaria. Brem[11] saw one patient who developed the disease after only two months' residence on the Isthmus of Panama; and Ziemann[12] one case occurring twenty-seven days after reaching the infected locality, and another within six weeks. Dr. Prado, in a personal communication, informs me that blackwater fever attacks new arrivals in Tobago.

It should be remembered that these patients had not resided previously in infected districts and that in most of them no history of a previous malarial infection could be obtained. It is thus evident that a long residence in the infected district is not necessary for the development of hemoglobinuric fever and that the statement of Christophers and Bentley that many months or years of exposure to the infection is required before blackwater fever can occur is unwarranted in the light of the evidence which has accumulated regarding this question.

While it is true that the disease may occur in individuals who have been exposed only a short time, it is also true that the vast majority of cases of this disease occur between the first and third years of residence, thus proving that length of residence favors the development of the disease. As the regions in which hemoglobinuric fever occur are also malarial, it follows that most of the victims of this disease have also suffered from malarial infection, but this does not prove that malaria is the etiological factor, as will be shown in the following section.

PREVIOUS MALARIAL INFECTION AND HEMOGLOBINURIC FEVER

A history of previous malarial infection may be obtained in a large majority of cases of hemoglobinuric fever, but not in all. Many instances have been reported of the occurrence of this disease in individuals who had never suffered from malaria, and in whom no plasmodia could be found at the onset of the disease. The fact that the disease occurs most frequently in malarial localities makes it inevitable that most patients suffering from it have previously suffered from malaria, or, indeed, may be suffering from both diseases at the same time, for, from what we know of this disease, it is very rare as compared with malaria, and therefore most patients residing long enough in a locality to develop the disease have already become infected with malaria. It has been asserted by the

10. Quoted by A. Plehn, Jour. Trop. Med. and Hyg., 1908, ii, 294.

11. Brem. W. V.: Malarial Hemoglobinuria, Jour. Am. Med. Assn., 1906, xlvii, 1992.

12. Zieman, H.: Malaria, Mense's Handbuch der Tropenkrankheiten, Leipsic, 1906, iii (Halband I), 270.

most ardent advocates of the malarial theory that not a single case is on record of the occurrence of hemoglobinuric fever in a patient who had not previously had malaria, but such an assertion can be made only by one who is but very little acquainted with the literature, for numerous cases are recorded in which the disease developed in healthy individuals within two or three months after reaching infected districts and in whom there had never been any symptoms of malarial fever. That in most of these cases the disease could not have been present in a latent form is proved by the fact that many of the patients came from countries where malaria was not present, especially from England, and had not been exposed during the sea journey. Such cases have been reported by Manson,[9] Sambon,[13] Cardamatis,[14] Curry,[15] Ritchie,[16] Murri,[17] Stalkarrt,[18] Daniels,[19] and many others. The theory of Stephens and Christophers[20] that the disease is due to an unstable condition of the blood brought about by repeated malarial infection is thus disproved. It is a well-known fact that many patients suffering from hemoglobinuric fever do not present the appearance and symptoms of malarial cachexia, although, if this theory were true, it would be expected that most malarial cachectics would develop hemoglobinuric fever. It is also a well-known fact that this disease may develop during the first outbreak of malaria, and Deaderick[21] states that while hemoglobinuric fever generally occurs only after repeated malarial attacks, it may develop during the first attack. It is more than probable that such instances are in reality combined malarial and hemoglobinuric fevers.

Again, if repeated malarial attacks result in an unstable condition of the blood which causes hemoglobinuria, it is justifiable to ask why it is that such an unstable condition occurs as the result of malaria, only in restricted localities. In some of the most intensely malarial regions known a person may suffer for years from repeated attacks of malaria, and yet never develop hemoglobinuric fever, the disease being unknown in these regions. I have already called attention to the fact that climatic and all other known conditions are the same in these regions as in the

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13. Sambon, L. W.: The Etiology and Treatment of Blackwater Fever, Jour. Trop. Med., 1899, i, 243, 262, 295.

14. Cardamatis: La fièvre bilieuse hémoglobinurique, Paris, 1902, Ed. 1.

15. Curry, Joseph J.: Blackwater (Hemoglobinuric) Fever, Jour. Am. Med. Assn., 1902, xxxviii, 1130.

16. Ritchie: Cited by Manson, Tropical Diseases, p. 235.

17. Murri: Cited by Deaderick, A Practical Study of Malaria.

18. Stalkarrt, W. H. S.: Hemoglobinuric Fever and Paludism, Brit. Med. Jour., 1899, ii, 654.

19. Daniels, C. W.: Rep. Malarial Com. Roy. Soc., London, 1901, Series 5, p. 46.

20. Stephens, J. W. W., and Christophers, S. R.: Rep. Malarial Com. Roy. Soc., London, 1901, Series 5, p. 17.

21. Deaderick, W. H.: A. Practical Study of Malaria, Philadelphia, 1910, Ed. 1.

endemic centers of hemoglobinuric fever, so that it is very difficult to explain this discrepancy on the malarial hypothesis. The advocates of this theory, however, have urged that unknown conditions may be present, but this is simply begging the question, and admitting that malaria differs in this respect from any other known disease. So far as I am aware, there is no acute infectious disease which gives rise to a striking symptom-complex in some regions, while in others this symptom-complex never occurs, although in the latter regions the disease is as intense and pernicious in character. Yet we are asked by the adherents of the malarial theory of the origin of hemoglobinuric fever to believe that malarial infection produces blackwater fever in certain districts, while in similar districts this symptom-complex never occurs, although the malarial infections are of the same type.

To one who has studied the literature, however, it is perfectly evident that repeated malarial infection is not necessary for the production of hemoglobinuric fever, as many instances of the disease have occurred in which past malarial infection could be definitely proven not to have existed. The reports of Murri, Mould, F. Plehn, and Gros, as well as others, prove that the disease may occur in persons who have never suffered from malaria, while those of F. Plehn, Goltman and Krause, and Brem, prove that it may occur during the first symptoms of a malarial infection. It is therefore justifiable to conclude that hemoglobinuric fever is not due to repeated attacks of malarial fever, and that in many instances no previous malarial infection has existed.

THE OCCURRENCE OF MALARIAL PLASMODIA IN HEMOGLOBINURIC FEVER

The presence of malarial plasmodia in the blood of a large proportion of patients suffering from hemoglobinuric fever is considered by many authorities as proving its malarial origin; but many other conditions are frequently encountered in malarial regions in which the plasmodia may be found in the blood, but which are never considered as being due to malarial infection. The fashion of considering an organism as causative merely because it is frequently associated with a disease has generally resulted in disaster, and in the case of kala-azar, Malta fever, and sleeping-sickness, greatly delayed the discovery of the real cause.

It is but natural that, in a malarial region, patients suffering from this disease should present malarial plasmodia in their blood in many instances. The mere presence of such plasmodia, or of pigment in the tissues, does not prove that the condition is due to malarial infection, and the absence of both pigment and plasmodia in well-authenticated cases of hemoglobinuric fever proves conclusively that malaria cannot be considered as the direct cause of the disease.

As regards the frequency of the occurrence of plasmodia in the peripheral blood in hemoglobinuric fever, it may be said that it varies in different localities and with the time that the blood is examined. I have collected 273 cases in the literature, of which 109, or 40 per cent., showed malarial plasmodia in the blood. The researches of Stephens and Christophers[4, 20] and of Mannaberg[22] have shown that the number of patients presenting plasmodia in their blood varies with the time of examination, 95 per cent. of patients showing them the day before the attack; 60 to 70 per cent. showing them the day of the attack; and only 17 to 20 per cent. showing them the day after the attack. This fact has been used in contradicting the proofs of the absence of the plasmodia in cases of hemoglobinuric fever, but there are many cases on record in which the blood was examined before, during, and after the attack, and no plasmodia could be found, even puncture of the spleen being attended with a negative result. While 95 per cent. of hemoglobinuric fever patients may show plasmodia in their blood in some regions the day before an attack, it is equally true that in other blackwater regions 100 per cent. have not shown them, for it must be remembered that it is but seldom that the blood happens to be examined at this time, and that, therefore, the number of observations are very small.

From the reports of many investigators it is justifiable to state that cases of hemoglobinuric fever have occurred in which malarial plasmodia were not present, so far as could be determined, either before, during, or after the attack, while in fatal cases no evidence of malarial infection was found at autopsy. Many of these cases are reported by staunch advocates of the malarial theory and the evidence, therefore, is not affected by an unconscious personal equation.

Poole[6] found that some of his cases were negative for plasmodia either before, during, or after an attack of blackwater, although the examination was made most carefully; Barratt and Yorke[23] carefully examined twenty cases of hemoglobinuric fever, and found that nineteen of them were negative for plasmodia on the first day of the disease. They say:

> On one occasion it happened that an examination of the blood was made within two hours of the establishment of hemoglobinuria and one hour before the administration of quinin. In this case no parasites could be recognized after careful search. It can be asserted, therefore, that in this case, hemoglobinuria was not dependent on the hemolysis, in the peripheral blood, of the red cells containing the parasites.

As regards the presence of pigment or parasites in the organs of fatal cases, Barratt and Yorke say:

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22. Mannaberg, J.: Die Malaria-Krankheiten, Nothnagel's Encyclopedia, Berlin, 1899.

23. Barratt, J. O. W., and Yorke, W.: An Investigation Into the Mechanism of the Production of Blackwater Fever, Ann. Trop. Med. and Hyg., 1909, Series T. M., iii, 152.

The presence of malarial pigment in the blood-vessels of the organs, usually the kidneys, has been described by several authors. In the three cases in which we had an opportunity of studying this point, no pigment was found in the kidneys, spleen, or liver, nor could malarial parasites be recognized in the blood-vessels of these organs.

In one of their cases the patient had never suffered from malaria to his knowledge. In sixteen of the twenty cases the onset of hemoglobinuria was preceded for several days by more or less general disturbance. Regarding this they say:

This lasted in fourteen attacks from one to seven days, and in two attacks ten and twenty-one days, respectively. The preliminary illness was regarded as malarial, but in only one case were malarial parasites found before the onset of hemoglobinuria.

This statement effectively disposes of the assertion that malarial plasmodia are always present in the peripheral blood before the onset of blackwater fever. Barratt and Yorke performed splenic puncture in six of their cases and in none of them were they able to find parasites or pigment in the material obtained; while they examined four of their patients on the first day of hemoglobinuria, giving the peripheral blood the most careful scrutiny, and did not find plasmodia in one of them.

Koch[24] described twenty-three cases of hemoglobinuric fever in which no plasmodia could be found, although some of them were fatal infections, while in four cases he found the plasmodia both before and after the attack, thus proving that their absence is not entirely due to blood destruction, as claimed by Christophers and Bentley. Koch says:

We thus perceive that the malarial plasmodia do not perish in blackwater fever attacks; that during the attack they are either entirely absent or show no remarkable increase; that, even if they are present in great numbers, no hemoglobinuria need develop. Therefore, how can one still assert that blackwater fever is caused by malarial parasites?

Mould[25] reports a case of hemoglobinuric fever which developed in a hospital; the patient, in whose blood no plasmodia could be found, never having suffered from malarial infection. Curry[15] reports two cases in which neither during the attack nor at autopsy could any evidence of present or past malarial infection be obtained, the tissues being free from pigment and parasites, and the blood likewise. In both cases the blood was examined during the first day of the attack. He describes another case in which no parasites were found, although the blood had been carefully examined for ten days preceding the attack.

Daniels[19] was unable to find plasmodia in a single one of sixteen cases which he investigated, either during or after the period of hemoglobinuria; Christophers and Bentley,[20] while agreeing that the manifestations of hemoglobinuric fever should occur only during coincident

24. Koch, R.: Blackwater Fever (Hemoglobinuria), Jour. Trop. Med., 1899, i, 333.

25. Mould, Captain: Cited by Sambon, Jour. Trop. Med., 1899, i, 243, 262, 295.

malarial infection, in their own report describe cases in which even the splenic blood did not contain parasites. Case 20 showed no parasites, though examined during the first day of the attack, and Case 26 was also negative, while the splenic blood of other patients showed a very few plasmodia. Their results dispose of the theory that the plasmodia are really very numerous in this disease, but are not discovered because they are localized in the internal organs, especially the spleen.

Newell,[26] though an ardent advocate of the malarial theory, did not find plasmodia in any of the five cases described in his book, so far as he states. Van der Scheer,[27] Hanley,[28] Thin,[29] Howard,[30] Oeconomou,[31] Le Dantec,[32] and Gauducheau,[33] all report cases in which plasmodia were not found in the blood during an attack of hemoglobinuric fever, and many of them were negative before the onset of hemoglobinuria.

Whipple[34] has recently contributed a valuable study of the pathology of hemoglobinuric fever, and believes that malaria always precedes this disease and predisposes to it, but the evidences of malarial infection in most of his cases are slight and would appear to be insufficient to prove the importance of previous malarial infection. He studied nine cases of hemoglobinuric fever at autopsy, in only two of which were plasmodia demonstrated, and compares the pathological findings with three cases of combined hemoglobinuric fever and pernicious malaria, and with five cases of pernicious malaria. He believes that the pathological findings in the hemoglobinuric fever cases "show a great similarity to those of the pernicious malaria cases and indicate that a malarial infection is an unfailing factor in all cases." In seven of the nine cases of uncomplicated hemoglobinuric fever the only evidence of malaria consisted in a small amount of pigment in the leukocytes of the spleen, kidney, and liver, and this pigment was present in such small amount in two cases that Whipple says (p. 226):

> In autopsy 1,168 and 1,169 malarial pigment is in very small amounts and is only found in the various organs after a long search. It is included in phagocytes. The second case shows a few coarse grains of malarial pigment in the cortex of the portal gland, indicating a previous malarial infection. We cannot imagine any ferment capable of rapidly dissolving the melanin which is set free by the sporulation or death of the malarial parasite. So it seems conclusive

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26. Newell, C.: Blackwater Fever (Bilious Malignant Tertian Ague), London, 1909, Ed. 1.
27. Van der Scheer: Cited by Mense: Arch. f. Schiffs- u. Tropen-Hyg., 1899, iii, 80.
28. Hanley: Jour Trop. Med., 1899, i, 85.
29. Thin: Brit. Med. Jour., 1900, ii.
30. Howard: Jour. Trop. Med., 1907, x, 81.
31. Oeconomou: Cited by Cardamatis, Progrès Méd., 1902, xx, 201.
32. Le Dantec: Pathologie exotique, Paris, 1905, Ed. 1.
33. Gauducheau: Cited by Deaderick, A Practical Study of Malaria.
34. Whipple, G. H.: Blackwater Fever and Pernicious Malaria in Panama, Malaria, 1909, i, 215.

that there could have been but very few malarial parasites in the vascular system of these two patients. This would indicate that blackwater fever may follow a very slight infection of malaria, and that the severity of the attack need necessarily bear no relation to the severity of the hemoglobinuria.

It would appear that to base a belief in the causative relation of previous malarial infection to hemoglobinuric fever on the finding of a few grains of malarial pigment at autopsy in individuals residing in a malarial locality such as the Isthmus of Panama, where Whipple made his investigations, is hardly warranted, for in most patients dying of any disease in such regions, the organs would undoubtedly show a few grains of malarial pigment. If, in such a case, death were due to yellow fever, it would hardly be justifiable to assert that the malarial pigment present proved that the disease was of malarial origin. As I have stated, numerous cases of hemoglobinuric fever are on record, in which, even at autopsy, both parasites and malarial pigment were absent from the blood and tissues. Major Walter D. Webb, Medical Corps, United States Army, retired, has recently handed me the notes of two cases of hemoglobinuric fever, observed by him, in which neither on the first day of the attack, nor at autopsy, could malarial pigment or parasites be found in the blood or in scrapings from the spleen or liver. In both of these cases the onset was sudden, while the individuals were in apparent health, and in one of the cases the patient stated that he had never suffered from malarial fever. The argument that in such cases as these the malarial infection may have been latent, is negatived by the fact that at autopsy the organs presented no evidence of malarial infection, and it is impossible for one to believe that this would be so had the patients suffered from latent malaria. In one of Webb's cases no quinin had been given before the attack.

The discordant results obtained by various observers as to the occurrence of malarial plasmodia in patients suffering from hemoglobinuric fever, and the proportion of patients showing the plasmodia before or during the attack, is very largely due to the fact that malarial infection is very much more prevalent in some blackwater fever regions than it is in others, and thus a much greater proportion of the inhabitants suffer from such infection. It appears to be most illogical to maintain that, because the plasmodia are found in a certain proportion of hemoglobinuric fever patients, the disease must be caused by these parasites, in view of the absolute proof that cases of the disease occur in which neither past nor present malarial infection has occurred. A single case of hemoglobinuric fever occurring in an individual who has never suffered from malarial infection, and in whom, even at autopsy, no trace of present or past infection can be demonstrated, should be enough to convince the most skeptical that malaria is not the cause of this disease, and many such cases are on record.

THE RELATION OF THE SPECIES OF MALARIAL PLASMODIA TO HEMOGLOBINURIC FEVER

A few authorities hold that hemoglobinuric fever is due to the estivo-autumnal plasmodia, or to a specific form hitherto undifferentiated. This theory is negatived by the fact that all species of malarial plasmodia have been found in the blood of patients suffering from this disease, and that the disease occurs in individuals in whom no plasmodia can be found either before, during, or after the attack of hemoglobinuria. It is, however, an accepted fact that the estivo-autumnal plasmodia are more frequently associated with hemoglobinuric fever than are the other species, but there are many cases reported in the literature in which the other species of plasmodia were found.

According to Deaderick,[21] the tertian plasmodium has been found in cases of hemoglobinuric fever by Ziemann, Panse, Orme, Pecori, Carducci, Van der Horst, Hughes, Koch (five cases), A. Plehn (three cases), Ollwig, McElroy, Goltman and Krauss, Brem, Herrick and Curl; while, according to the same authority, the quartan plasmodium has been found associated with this disease by Vincenzi, Grocco, Kleine, Kudicke, and Otto. These observations prove that, if this disease be due to malarial infection, it may be produced by any of the species of plasmodia, and that the more frequent occurrence of the estivo-autumnal plasmodia does not prove them to be the cause of the disease, any more than the more frequent occurrence of these species of plasmodia in kala-azar patients proves them to be the cause of that disease.

As regards the presence of an undifferentiated species of malarial plasmodium, the fact that the disease occurs associated with all of the known species of plasmodia is conclusive proof that such a species is not necessary, and, in addition, all of the plasmodia associated with this disease have been very carefully studied by eminent authorities and have not been found to differ from those usually observed in malarial infection.

The theory that hemoglobinuric fever is merely one of the forms of pernicious malaria, which is held by many French and American observers, is negatived by the fact that this peculiar form of pernicious malaria occurs only in restricted localities, and that it is absent in many regions where the worst forms of pernicious malaria occur. Koch first thoroughly disproved this theory and anyone who cares to study the literature will become convinced that it is untenable in the face of the evidence that has accumulated against it.

CHANGES IN THE BLOOD IN HEMOGLOBINURIC FEVER

The blood examination in patients suffering from hemoglobinuric fever generally demonstrates an increase in the large mononuclear leukocytes, and frequently the presence of pigmented leukocytes. The increase

in the large mononuclear cells has been used as a weighty argument in favor of the malarial nature of the disease, but it is perhaps the weakest of all the arguments used by the advocates of this theory. While an increase in these cells occurs in both malaria and hemoglobinuric fever, a similar increase is more or less characteristic of other acute infectious diseases, and occurs almost constantly in sleeping-sickness, kala-azar, and recurrent fever. The fact that an increase in these cells occurs in black-water fever simply suggests that the disease may be caused by a protozoon, and is really a better argument for the specific theory than for the malarial theory.

The presence of pigmented leukocytes has little value, as they occur in the vast majority of individuals residing in intensely infected malarial localities, and sometimes persist for weeks after all other traces of malarial infection have disappeared. While the presence of pigmented leukocytes indicates that at some time the patient has suffered from malarial fever, it is very slender proof of the malarial nature of hemoglobinuric fever.

AUTOLYSIS AND THE PRODUCTION OF HEMOGLOBINURIC FEVER

Since the remarkable development of our knowledge regarding hemolytic phenomena, the theory that an autolysin is produced in the blood of certain individuals by repeated attacks of malaria, thus leading to the production of hemoglobinuria, has become a favorite one, and is held by many observers, notably Deaderick, Bignami, Cassagrandi, and Christophers and Bentley. None of the believers in this theory have been able to demonstrate conclusively the presence of an autolysin in the blood of patients suffering from hemoglobinuric fever, although every effort has been made to do so. The theory is disproved by the fact that this disease occurs in persons who have not suffered from repeated malarial attacks, and that autolysins have not been demonstrated in the blood of man either in health or disease.

Some of the theories regarding the production of this theoretical autolysin are very complicated, but they are all negatived by the recent work of several observers who have failed to find such a body in the blood of patients suffering from hemoglobinuric fever, or in that of patients suffering from other diseases. The work of Dudgeon and Wilson,[35] Moss,[36] and Barratt and Yorke,[23] is of great interest in this con-

35. Dudgeon, L. S., and Wilson, H. A. F.: On the Presence of Hemagglutinins, Hemopsonins and Hemolysins in the Blood Obtained from Infectious and Non-Infectious Diseases in Man, Quart. Jour. Med., 1910, iii, 285.

36. Moss, W. L.: Studies on Iso-agglutinins and Isohemolysins, Bull. Johns Hopkins Hosp., 1910, xxi, 63.

nection. Dudgeon and Wilson found that, while some samples of normal serum have the power of agglutinating almost all specimens of normal red corpuscles, in no case were they able to find auto-agglutination or autohemolysis in normal blood. In blood from disease they were unable to find a single instance of autohemolysis, even in twenty-one cases of pernicious anemia, in which, as they say: "of all diseases it might well be imagined that autohemolysis could be demonstrated, but a negative result was obtained in every instance."

The very thorough work of Moss demonstrates beyond question that autohemolysis does not occur in either health or disease, and it is a significant fact that he found no constant differences between the agglutinating and hemolyzing qualities of serum in health and disease, which one would expect to find did disease tend to bring about an unstable condition of the blood leading to autohemolysis. Moss did not observe auto-agglutination in any of the 213 individuals that he studied, while autohemolysis was observed but once, and of this instance he says: "In the latter case the hemolysis may have been due to extraneous causes." He found that all of the serums investigated contained an antihemolysin which protected the homologous corpuscles.

Barratt and Yorke, in their recent and conclusive experiments regarding hemolysis in hemoglobinuric fever, were not able to demonstrate an autolysin in any of twenty-one cases which they investigated, while, in the eleven cases they examined as to the presence of an isolysin, but one gave a positive result. They conclude:

> From these experiments the important conclusion follows that the mechanism of production of blackwater fever stands in an altogether different category from that of paroxysmal hemoglobinuria. The presence of hemolysin or of defect of antilysis, which is present in the latter case, is absent in blackwater fever, where, therefore, search must be made for other factors.

These authors examined the blood of two oxen suffering from Texas fever, and of two dogs suffering from piroplasmosis, and were unable to find an autolysin in the blood of any of them. This fact is significant as showing the probable relationship of these infections to hemoglobinuric fever, a relationship which has been noted by many investigators.

Whipple,[34] as the result of careful experiments, also reaches the conclusion that the blood of hemoglobinuric fever patients does not contain any hemolysin.

It will thus be seen that the presence of an autolysin in the blood in hemoglobinuric fever has been disproved, and, even were such a body present, the advocates of the malarial theory would still have to explain why malarial infection produced it in some localities and never produced it in others. In other words, the presence of such a body in the blood of hemoglobinuric fever patients would point toward its specific nature rather than toward the malarial theory.

2. QUININ AND HEMOGLOBINURIC FEVER

The theory that hemoglobinuric fever is due to quinin will be considered but briefly, as it is not strictly included in the subject for discussion. This theory endeavors to explain the etiology of the disease by assuming that, in certain individuals, the administration of quinin is followed by hemoglobinuria, or that this results if the drug is administered to one who has suffered from repeated malarial attacks. Veratas, a Greek physician, suggested this explanation of the disease in 1858, and in 1874, Tomaselli gave it his support. The theory is believed in by many authorities, especially by Koch, whose support was accepted for a while as almost conclusive proof of its truth. As a matter of fact, many instances of hemoglobinuric fever have been reported in individuals who had never taken quinin, while the theory that the long-continued use of the drug for malarial infection may produce the disease is negatived by the fact that thousands of individuals take quinin, at intervals, for years, and never develop the disease except in regions where hemoglobinuric fever is endemic.

The occurrence of the disease in patients who have never taken quinin has been reported by A. Plehn,[5] in twenty-two cases; Cardamatis,[14] in thirty-two cases; Shropshire,[37] in twenty-five cases; Seal,[38] in six cases, and by many other observers.

My experience among the Filipinos positively disproves this theory, for of the hundreds of cases of malarial fever which I studied among these people, most of whom had suffered for years, at intervals, from malaria, the administration of quinin was not followed in a single instance by hemoglobinuria.

In the thousands of cases of malaria I have observed in soldiers of the United States Army, all of them treated with large, and frequently, heroic doses of the drug, I have observed but two cases of hemoglobinuria following its use, and in both the symptomatology was very different from that of hemoglobinuric fever. In those instances in which hemoglobinuric fever occurs among the natives of an endemic region, and many instances of this kind are on record, in hardly a single case had quinin been administered before the attack, and this must be true of the occurrence of the disease in any region where the drug is not in use by the native race.

It must be remembered that this disease occurs in malarial localities and that those suffering from the prodromal symptoms almost always take quinin, believing that they are suffering from malaria, and thus the

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37. Shropshire, W.: Hemoglobinuric Fever, Its Causes and Treatment, with Especial Reference to the Use of Quinin, Jour. Am. Med. Assn., 1903, xli, 600.

38. Seal, C. E. B.: Notes on a Few Cases of Hemoglobinuria in India, Jour. Trop. Med., 1899, i, 179.

hemoglobinuria which follows is quite naturally considered as being due to the drug.

It is true that quinin does produce hemoglobinuria in some individuals, but in such instances the symptoms following each administration of the drug may occur in regions in which hemoglobinuric fever is unknown, and differ very much from the classical symptoms of hemoglobinuric fever. These cases should not be used as an argument in favor of the etiological relationship of quinin to this disease.

If quinin be the cause of this disease, it would be expected that the administration of it to patients suffering from an attack would result in an increase in the intensity of the symptoms and that death would follow in the majority of the cases. This is not so, however, for there is undisputed evidence that the mortality is very little higher when quinin is administered than when it is not. Deaderick[39] says:

> The great majority of cases recover even under the continued use of large doses of quinin.

It is also true that the severity of an attack of hemoglobinuric fever bears no relation to the size of the doses of quinin that have been administered, nor do large doses given during the attack result in a greater percentage of deaths than small ones. Shropshire[40] reports sixty-one cases treated with less than 5 grains per day, with 26.2 per cent. mortality; while in 141 cases treated with over 20 grains per day, the mortality was only 16.9 per cent. Crosse[41] states that in his experience the administration of the drug does not aggravate the attack, and that on the Niger all hemoglobinuric fever patients are treated with quinin and a large percentage recover. Moffatt[42] details six cases in which from 60 to 120 grains of quinin were given daily and all the patients recovered; while Robson[43] has given 60 grains of the drug at a single dose with good results.

Some authorities believe that quinin produces the disease only in certain individuals having an idiosyncrasy to the drug; but if this be true, we must believe that such idiosyncrasy occurs only in certain localities, for the drug is given in large doses, for long periods of time, all over the world, but hemoglobinuric fever only occurs in limited localities.

Barratt and Yorke[23] in their recent work on the mechanism of blackwater fever reach the following conclusions regarding the effect of quinin on the blood:

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39. Deaderick, W. H.: A Practical Study of Malaria, Philadelphia, 1910, Ed. 1, p. 165.
40. Shropshire: Med. Rec., 1903, lxiii, 798.
41. Crosse: Blackwater Fever, London, 1899, Ed. 1.
42. Moffatt: Brit. Med. Jour., 1898, i, 926.
43. Robson: Brit. Med. Jour., 1898, i, 1287.

Owing to the toxicity of quinin, its concentration in the blood cannot reach an amount sufficient to allow of its direct hemolytic action on the red cells taking place during life. The red cells during blackwater fever are not hemolyzed by quinin bihydrochlorid more readily than in health.

Again, some authorities believe that hemoglobinuric fever is produced by quinin only when a person who has been taking the drug for a long time suddenly ceases to take it, and then takes a very large dose. This is disproved by the fact that this method of taking quinin is common throughout the world, while hemoglobinuric fever is restricted in its distribution; also by the fact that the disease occurs in individuals who have never taken the drug.

From this summary of the evidence against the quinin theory of the etiology of hemoglobinuric fever I believe that it is evident that quinin *per se* is not the cause of the disease. The facts that the drug is given throughout the world in large doses to individuals suffering from malarial infections, while hemoglobinuric fever occurs only in restricted localities; that many patients suffering from the disease recover under the administration of the drug; that patients who have apparently suffered from hemoglobinuria produced by quinin do not generally relapse when the drug is given; that there exists no relation between the amount of quinin given and the severity of the disease; that the disease occurs in individuals who have never taken quinin; and that the red blood-corpuscles of patients suffering from hemoglobinuric fever are as resistant to the drug as are the red cells of the normal individual, all point conclusively to the opinion that quinin cannot be regarded as the cause of hemoglobinuric fever.

3. THE SPECIFIC THEORY OF THE ETIOLOGY OF HEMOGLOBINURIC FEVER

PRESENT STATUS OF THEORY

From the evidence which has accumulated regarding the relationship of malaria and quinin to hemoglobinuric fever, it would appear that we cannot with justice regard either as being the etiological factor in the production of the disease, and that, therefore, we must consider the etiology of this disease as still undecided. This being so, it is but natural that many authorities have endeavored to prove that hemoglobinuric fever is a distinct disease due to a specific organism, and it must be admitted, that there is much evidence which points to such a conclusion. As early as 1892, Manson,[44] in an address delivered before the Epidemiological Society of London, stated that he believed hemoglobinuric fever to be a distinct disease; but it is chiefly to Sambon that we owe the awakened

44. Manson, Sir Patrick: Tr. Epidemiol. Soc., 1892-1893, xii, 384.

interest in the specific theory of the disease. In two excellent papers[45] this author has called attention to the inadequacy of the malarial and quinin theories and collected the evidence in favor of the specific nature of the disease. At the present time this theory is steadily gaining ground, its most ardent advocates being Manson, Sambon, Rho and Blanchard, while numerous other investigators concede that only by admitting the specific nature of the disease can the contradictions inherent in the other theories be explained. Every evidence which has been urged for the malarial nature of the disease can be used as well in advocating its specific nature, and, in adidtion, there are certain positive facts which can be accounted for only by admitting that the disease is due to some hitherto undescribed parasite.

GEOGRAPHICAL DISTRIBUTION

As I have already pointed out, the geographical distribution of this disease is a much stronger argument for its specific nature than for the malarial theory. The fact that the disease occurs only in malarial localities simply proves that the parasite causing it finds in such localities the conditions necessary for its development or transmission, and the limited distribution of the disease in even the most malarial localities speaks still more strongly for its specific nature. The geographical distribution of kala-azar is very like that of hemoglobinuric fever, so far as its limitation to certain districts is concerned, and the latter disease, so far as I know, also occurs only in malarial localities. There are other acute infectious diseases which are still more limited as regards distribution, for instance, Rocky Mountain spotted fever, which occurs only in very restricted localities in our own country, and the tsutsugamushi disease, or flood fever of Japan, which occurs only in certain small districts along the course of rivers in northern Japan. Sleeping-sickness is another disease which occurs only in malarial localities, but we do not believe, because of its geographical distribution, that it is due to malaria.

The fact that the disease occurs in patients who have never suffered from malaria or taken quinin, and in whom, even at autopsy, no trace of past or present malarial infection can be demonstrated, is positive proof that it is not due to either of these factors, and speaks in favor of its specific nature.

The occurrence in the endemic regions of hemoglobinuric fever of certain small areas, and of certain houses in which the disease is most frequently observed, points very strongly to a specific cause and probably indicates that in such places there exist certain factors which enable the disease to be transmitted. It is evident that hemoglobinuric fever is a

45. Sambon, L. W.: Blackwater Fever, Jour. Trop. Med., 1898, i, 70; The Etiology and Treatment of Blackwater Fever, Jour. Trop. Med., 1899, i, 243, 262, 295.

comparatively rare disease, even in its endemic centers, and this fact again points to its specific nature, rather than to its being due to malaria, and indicates that the cause is some parasite which requires very particular conditions either for development or for transmission.

DISPROPORTION BETWEEN NUMBER OF MALARIAL AND HEMOGLOBINURIC FEVER CASES

The numerical disproportion between the cases of hemoglobinuric fever and of malaria, in even the worst endemic regions of the former, is a strong argument in favor of the distinct nature of this disease. No one will deny that the number of cases of hemoglobinuric fever occurring in any locality when compared with the number of malarial infections is very small; while in many regions hemoglobinuric fever is unknown, although thousands of cases of malaria occur every year. In Greece, Pampoukis observed 34,937 cases of malaria, of which only 0.7 per cent. presented hemoglobinuria; Burot and Lagrand[46] observed 559 fatal cases of malaria, and only five of hemoglobinuric fever; and Stalkarrt[18] observed many cases of severe malarial infection without seeing a case of hemoglobinuria. There are many localities in which hundreds of cases of malaria occur yearly and yet hemoglobinuric fever is so rare as to be regarded as a medical curiosity. The army statistics regarding this question are of the greatest interest and value. It should be remembered that these statistics deal with soldiers recruited from every portion of our country, and include men who have served in the United States, in Cuba, Porto Rico, and the Philippines. Table 4, compiled from the Reports of the Surgeon General of the Army, shows the number of admissions to army hospitals from malaria and hemoglobinuric fever from 1903 to 1908 inclusive.

TABLE 4.—MALARIA AND HEMOGLOBINURIC FEVER IN THE UNITED STATES ARMY FROM 1903 TO 1908, INCLUSIVE

	Admissions for — Entire Army —		Admissions for U. S., Cuba, Hawaii, Porto Rico and Alaska		Admissions for —— Philippines ——	
Year.	Malaria.	Hemoglobinuric Fever.	Malaria.	Hemoglobinuric Fever.	Malaria.*	Hemoglobinuric Fever.
1903.....	13,608	0	2,685	0	10,923	0
1904.....	4,955	0	2,170	0	2,785	0
1905.....	4,833	2	1,942	1	2,891	1
1906.....	6,077	3	2,042	1	3,766	2
1907.....	3,395	1	1,280	1	1,963	0
1908.....	3,030	0	1,424	0	1,484	0
Totals ..	35,898	6	11,543	3	23,812	3

* Of the 23,812 admissions from malaria in the Philippines at least 11,000 were due to the estivo-autumnal plasmodia.

46. Burot and Lagrand: Cited by F. Plehn, Tropenhygiene, Jena, 1906, Ed. 1.

It will be seen from Table 4 that, during the six years which it covers, there were 35,898 admissions from malaria in the entire army, and only six admissions from hemoglobinuric fever, while the fact that hemoglobinuric fever does not occur among the Filipinos, although malaria is a very common and severe disease among these people, is well shown in Table 5, which gives the number of admissions from malarial fever and hemoglobinuric fever, from 1903 to 1908, inclusive, in the Philippine Scouts, an organization composed of native Filipinos from all parts of the Islands.

TABLE 5.—MALARIA AND HEMOGLOBINURIC FEVER IN THE PHILIPPINE SCOUTS FROM 1903 TO 1908, INCLUSIVE

Year.	Admissions from Malaria.	Admissions from Hemoglobinuric Fever.
1903	2,565	0
1904	1,691	0
1905	2,710	0
1906	1,871	0
1907	1,463	0
1908	1,205	0
Totals	11,505	0

From the above table it is seen that while there were 11,505 admissions from malarial fever among the Philippine Scouts during the six years mentioned, there was not a single admission from hemoglobinuric fever. If these figures are added to those for our army, exclusive of the scouts, there are 47,403 admissions from malarial fever with but six admissions from hemoglobinuric fever, or 0.00012 per cent.

In my own experience, covering over ten years' observation of the malarial fevers, during which time I have had the opportunity of studying nearly 6,000 cases of malaria in which the plasmodia were demonstrated in the blood, I have observed only two cases of hemoglobinuria, and in both of these the symptoms were not typical of true hemoglobinuric fever. All of the malarial cases were observed in Cuba or the Philippines, or in the United States in soldiers returning from service in these countries, and almost every one of them had suffered from repeated attacks of malarial fever, fully two-thirds of them from estivo-autumnal infections. In view of these facts, is it possible to believe that hemoglobinuric fever is due to malarial infection? It appears to me that this great disproportion between the number of cases of malaria and hemoglobinuric fever is very strong proof of the specific nature of the latter disease.

OCCURRENCE IN EPIDEMICS

The occurrence of epidemics of hemoglobinuric fever is proof of its specific nature. While there are many instances of the occurrence of epidemics of malarial fever, there are no instances of epidemics of a special symptom-complex associated with this disease, and this is what

hemoglobinuric fever is believed to be by the advocates of the malarial theory. Epidemics of this disease have been reported by various observers. Sambon[13] recalls the epidemic which occurred among the laborers on the Isthmus of Corinth, and the Chinese laborers on the Congo railway; and the same disease has occurred in epidmic form on the Isthmus of Panama during the French operations on the canal. According to Dr. Wenyon[47] the disease ravaged like a plague the Chinese army on the Tonquin border of Kwansi, and the same authority instances an outbreak in a prison in Sardinia, in which twenty-four out of 800 convicts suffered from the disease. According to A. Plehn,[48] hemoglobinuric fever not infrequently occurs in epidemic form in Africa, and he mentions several such instances. In this relation may be mentioned the instances already quoted, in which several individuals in the same house develop the disease, although those living in the surrounding buildings do not suffer.

The fact that hemoglobinuric fever occurs in regions where the natives are immune to malaria is an argument for the specific nature of the disease. We are informed on the authority of A. Plehn that the negro of Africa is not immune to hemoglobinuric fever; and Doering,[49] F. Plehn,[50] and others have observed cases among the negroes of that country. It is generally accepted as proved by the researches of Koch and others that the natives of certain malarial regions in Africa, after reaching adult life, are immune to malaria, and Koch did not find the plasmodia in 100 per cent. of the adult natives whom he examined. How can we reconcile these two facts, if hemoglobinuric fever be due to malarial infection? Is it not more reasonable to believe that we are dealing with a distinct disease, due to a specific parasite?

SYMPTOMATOLOGY AND PATHOLOGY

The symptomatology of hemoglobinuric fever is distinctive and unlike that of any form of malarial fever with which we are acquainted. The lack of periodicity in the temperature curve, the presence of an enlarged and tender liver, the repeated chills, the occurrence of marked jaundice, the leukocytosis, and the hemoglobinuria, have all been instanced by Sambon[13] and other authorities, as definitely separating the disease on clinical grounds from malarial fever. The fact that, in relapses of this disease, the symptom of hemoglobinuria is always repeated proves that we are not dealing with a pernicious form of malaria, for relapses of pernicious malaria are not always accompanied by the same

47. Wenyon: Cited by Sambon, The Etiology and Treatment of Blackwater Fever, Jour. Trop. Med., 1899, i, 243, 262, 295.

48. Plehn, A.: The Cause, Prevention and Treatment of Hemoglobinuric Fever in Warm Countries, Jour. Trop. Med. and Hyg., 1908, xi, 294.

49. Doering: Cited by Deaderick, A Practical Study of Malaria.

50. Plehn, F.: Arch. f. Schiffs. u. Tropen. Hyg., 1904, iii, 336.

symptoms. While the prodromal symptoms of hemoglobinuric fever cannot be differentiated from those of malaria, the symptoms of the fully developed attack are distinctive.

The pathologic changes in hemoglobinuric fever is very strong proof of its specific nature, for the lesions are not those of pernicious malarial fever. Even the most ardent advocates of the malarial hypothesis admit that cases occur in which not even a few grains of malarial pigment can be found in the viscera, and there is no evidence of either present or past malarial infection. It is generally conceded that, unless the lesions of a disease are found at autopsy, it is not justifiable to believe the cause of death to be due to that disease, and it would appear that it is fully justifiable to disregard the malarial theory of hemoglobinuric fever because of the pathological lesions present in fatal cases. The absence of malarial pigment or parasites in the organs, or in the blood in many cases, the condition of the kidneys, which is seldom simulated in pernicious malaria, the enlarged, but unpigmented liver and spleen, are all very different from the lesions usually observed in fatal malarial infections. The enlargement of the spleen in uncomplicated cases of hemoglobinuric fever is exactly similar to that occurring in most infectious diseases, and is no proof of its malarial origin. One would think that, after the disastrous experience regarding the significance of splenic enlargement in kala-azar, it would not again be urged as an argument for the malarial etiology of any disease, but in the case of hemoglobinuric fever it is still so used. In his study of the pathology of this fever Whipple[34] gives very completely the lesions he found in nine cases of this disease, lesions which are certainly not those encountered in the vast majority of fatal cases of malarial fever. He calls attention especially to the occurrence of extensive areas of necrosis in the viscera, especially the spleen, and, while small areas of focal necrosis are sometimes found in the spleen, liver, and other organs in pernicious malaria, they are not peculiar to malarial infections, but occur also in diphtheria, streptococcus septicemia, and other acute infections in which a toxemic condition is present. The fact that they are much more pronounced in hemoglobinuric fever would appear to prove that the etiology of this disease is not that of malarial infection.

The occurrence of necrosis of the Malpighian bodies of the spleen, spoken of by Whipple, and which, according to this author, involves almost every Malpighian body in that organ, is never found in malarial infections in my experience, and alone serves to differentiate that disease from any form of such infection. It is impossible to read Whipple's excellent account of the pathology of hemoglobinuric fever without concluding that it is not due to malarial infection, for, while the two conditions have some things in common from a pathological standpoint, the

pathology of other tropical infections, such as yellow fever and kala-azar, have as much in common with malaria as does this disease. The presence of a small amount of malarial pigment cannot be held as proving the etiological importance of malarial infection, for the same pigment is found in patients dying of other diseases in malarial localities, and, as has already been shown, many cases are on record in which at autopsy no pigment could be found.

APPARENT ABSENCE OF PARASITE

One of the arguments brought forward against the specific theory of the origin of hemoglobinuric fever is the fact that, although it has been carefully searched for, no one has been able to demonstrate a parasite which could be considered as being the cause of the disease. I am sure that all will agree with me when I say that such an argument is valueless. There are a number of infections in which the cause has not as yet been demonstrated, yet one never uses this argument as valid evidence against their specific nature. Yellow fever, dengue, Rocky Mountain spotted fever and nearly all of the eruptive fevers belong in this category, and I believe that further research will show that many of these diseases are caused by a class of organisms very closely related and probably of protozoan nature.

There are many explanations for the apparent absence of a parasite from the blood and tissues in hemoglobinuric fever, among which may be mentioned a possible cyclical appearance of the parasite in the blood; the small number in the blood at any one time; the location of the parasite in some internal organ from which it rapidly disappears after the death of the patient; and the fact that the organism may be ultramicroscopical in size. The recent researches of Miyajima[52] on a piroplasma found in the blood of cattle in Japan, and of Crawley[53] on a trypanosome occurring in the blood of our own cattle, are of interest and significance in this relation. Both of these organisms occur in such small numbers in the blood of their respective hosts that they cannot be demonstrated in that fluid with the microscope, but, if the blood be added to suitable culture media, it is possible to secure the organism in pure culture. The same may be true of hemoglobinuric fever. The parasite may be present in such small numbers that a microscopic examination of the blood will not reveal it, but cultural methods might result in success. Curiously enough, I can find no record in the literature of an endeavor to make blood cultures in this disease.

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52. Miyajima, M.: On the Cultivation of a Bovine Piroplasma, Philippine Jour. Sc. B. Med. Sc., v, 83.

53. Crawley, H.: *Trypanosoma americanum*, N. Sp., A Trypanosome which Appears in Cultures Made from the Blood of American Cattle, Bull. 119, Bureau of Animal Industry, Dept. Agri., Washington, 1909.

CONCLUSIONS

That hemoglobinuric fever is not due to malaria I believe to be proved by its geographical distribution; by the fact that it occurs in individuals who have never suffered from malaria; and by the fact that, in many instances, neither before, during, or after an attack can plasmodia be demonstrated in the blood, while, even at autopsy, no trace of malaria can be found.

That the disease is not due to quinin is proved by the fact that it occurs in individuals who have never taken the drug, and that in many regions where the drug is extensively used the disease is unknown.

For the following reasons I believe that it is due to a specific organism: its geographical distribution; its numerical disproportion to malaria wherever it occurs; its occurrence in epidemics; the character of the pathological lesions; its symptomatology; the lack of conclusive evidence that it is due to malaria; and its analogy with other well-known infectious diseases.

In concluding I desire to call attention to the peculiar relation that this disease apparently bears to the hemoglobinuric fever of cattle and to piroplasma infections in general. That hemoglobinuric fever resembles Texas fever in its symptomatology has often been noted, and there is much reason to believe that it may be due to a similar parasite, for it is a significant fact that some form of piroplasma infection has been observed in almost every region in which blackwater fever is endemic. That no piroplasma has as yet been demonstrated in the blood in this disease does not count for anything, for it may be so small as to be indistinguishable by our present lenses, or it may occur in such small numbers as to necessitate its demonstration by cultural methods. All of the parasites belonging to this class are very minute and it is not at all improbable that the parasite of hemoglobinuric fever is ultramicroscopical in size, as we believe the parasites of yellow fever, dengue, and other diseases to be. Hemoglobinuric fever is probably transmitted by an insect, perhaps a larval tick, as is the case in tsutsugamushi disease, or the adult insect, as in Rocky Mountain spotted fever; but, whatever insect is ultimately proved to be the transmitting agent, we may feel sure that it will be one of comparatively rare occurrence, or that the conditions necessary for the transmission of the disease are peculiar, either in the cycle of development of the parasite in its insect host, or in the manner in which it reaches the insect. Only in some such manner can the comparative rarity of the disease in regions in which it is endemic, and its absence from others, be explained.

I would also call attention to the extremely small number of experiments which have been made on animals in research work on this disease. It is most unfortunate that the majority of investigators who have

worked on the etiology of hemoglobinuric fever have been strongly biased in favor of either the malarial or quinin theories, and have not considered animal experimentation necessary in solving the problem. That such experimental methods are of the greatest value in medical research, and absolutely indispensable, if our work is to be crowned with success, has been well shown by the results which have recently been accomplished in the study of dengue, typhus fever, Rocky Mountain spotted fever, and acute poliomyelitis.

Let us attack the problem of the etiology of this disease in a similar manner and I believe that it will not be long before we shall be able to prove beyond question that hemoglobinuric fever is a disease *sui generis* and not a manifestation of malaria.

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